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Determinants of Heterogeneous Adherence to HIV-Antiretroviral Therapies in the Multicenter AIDS Cohort Study

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Summary: Assessment of adherence to HIV antiretroviral therapy (ART) is required for studying therapeutic effectiveness and identifying subgroups needing focused education. The study's goals were to describe the level of ART adherence using self-reported recall over a 4-day period and to characterize determinants of lower adherence. The interaction between adherence and drug holidays on level of HIV RNA also was investigated. Perfect self-reported adherence was defined as taking all doses and numbers of pills as prescribed for current HIV medications. Independent predictors of <100% adherence were determined using multivariate logistic regression. Among 539 men, 419 (77.7%) were 100% adherent by the algorithm using self-reported data. HIV-1 RNA was <50 copies/ml in 48.2% of the adherent group versus 33.7% in the less adherent group ($p = .015$). This proportion dropped to 28% if a drug holiday was reported in addition to lower adherence. A drug holiday was not virologically detrimental if the participant was otherwise adherent. Determinants of lower adherence included African American race (odds ratio [OR], 2.4; $p = .008$), income <U.S.$50,000 (OR, 2.2; $p = .002$), no outpatient visits (OR, 3.6; $p = .003$) and increasing numbers of ART medications (OR, 4.5; $p = .001$). These data support the validity of using a questionnaire to assess adherence in observational studies. Identification of individuals with characteristics associated with lower adherence provides the basis for interventions to enhance adherence and optimize effective therapies. **Key Words:** Medication adherence—Antiretroviral therapy—HIV-1—Cohort studies.

The development and rapid widespread use of highly active antiretroviral therapies (HAART) among HIV-infected individuals have had a major impact on survival, immune function, and overall quality of life (QOL) (1–4). However, strict adherence to prescribed medication usage is critical for long-term effectiveness of antiretroviral therapy (ART) (5). Multiple factors including depression, alcohol and drug use, work schedules, changes in daily routines, and cognitive decline may impact on the ability to adhere to these complicated regimes. Individual consequences include declining immune function leading to risk of disease progression, clinical events, and death (3,6). Poor adherence may lead to drug-resistant HIV in the individual, limiting the effectiveness of therapy (6–8). With increasing use of these regimens in the population but at suboptimal levels, the prevalence of drug-resistant viruses will increase, which suggests that suboptimal adherence could have deleterious consequences at the individual and population level. Recent studies have found that anti-viral–resistant HIV can be transmitted (9,10). Given the importance of maintaining very high adherence to HAART, controversy surrounds clinical decision making regarding the optimal time to initiate potent therapy, for example, among patients who are unable to make a commitment to adhere to a rigorous medication schedule.

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It is important to measure adherence in the community in which the drugs are being used and in settings in which the individual will not fear negative social consequences of admitting lower adherence, which may happen in the physician's office or in the clinical trial setting. Previous studies have shown that it is difficult to evaluate adherence (11,12). Long-standing cohort studies in which a trust has developed between the staff and participants provide a more ideal arena for obtaining this information.

To date, the determinants, measurements, and interventions to improve adherence are poorly characterized and understood, and more research on this critical topic is needed (13). In this study, we provide an estimate of ART adherence in an established cohort study and examine characteristics associated with lower adherence to ART.

METHODS

Population: Multicenter AIDS Cohort Study

The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective study of the natural history of HIV infection in 5,622 homosexual or bisexual men, conducted since 1984 in four centers located in Baltimore (MD), Chicago (IL), Pittsburgh (PA), Los Angeles (CA). The men were observed at 6-month intervals with interviews, physical examinations, QOL assessments, neuropsychological testing, and blood sample collections to measure laboratory markers. The interview included questions about HIV and AIDS symptoms, use of antiretroviral medications, sociodemographic factors, and health care use. Further details about recruitment and characteristics of the cohort have been reported previously (14–16). The population was restricted to men who completed the MACS medication adherence questionnaire at Visit 30 (October 1998–March 1999). The institutional review boards of each center approved study protocols and informed consent was obtained from each participant.

Antiretroviral Medication Adherence Measurement

A questionnaire to ascertain adherence to antiretroviral medications was incorporated into the MACS protocol as of October 1998 (Visit 30). After piloting the form in 26 MACS participants, all HIV-1–seropositive men who reported using ART were interviewed by trained staff at Visit 30 using the modified medication adherence form. Adherence data were captured for all ARTs currently being taken by the participant at the time of the clinic visit. There is little data to suggest that patients can accurately recall missed doses beyond a few days (17). Therefore, focusing on recent adherence maximizes the participant's recollection. It has been shown that capturing data 1 day prior to the questionnaire administration is the most reliable for self-report (18). During the pilot study of the AACTG Adherence Instruments, it was found that asking about adherence over a 4-day period was optimal because it increased the likelihood of including a weekend day while still capturing data "yesterday" (19). The adherence measures used in the MACS were adapted from the Adult AIDS Clinical Trial Group's (AACTG) survey, which asks patients how many medication doses they missed during the previous day, 2 days, 3 days, and 4 days (17,19).

Questions on the MACS adherence form were either drug-specific or related to overall ART use. Drug-specific questions included adherence with dose intensity and frequency.

1. "According to your doctor, how many times a day should you take the medication?"
2. "How many times did you take the medication...yesterday? . . . 2 days ago? . . . 3 days ago? 4 days ago?"
3. "Is this pattern of use typical of your recent use of the medication?"
4. "Was there any time in the last 4 days that you took fewer pills per dose than were prescribed?"

Other questions related to overall antiretroviral usage (i.e., were not drug specific). These items considered compliance with scheduling and instructions for overall use.

1. "Most anti-HIV medications need to be taken on a schedule, such as 2 times a day or every 8 hours. How closely did you follow your specific schedule over the last 4 days?"
2. "Do any of your anti-HIV medications have special instructions such as take with food or take on an empty stomach or take with plenty of fluids? How often did you follow those special instructions over the last 4 days? Do any of these special instructions conflict?"
3. "Why have you missed taking your current medications?"

The level of self-reported adherence was dichotomized as 100% adherence or <100% adherence. Individuals were categorized into these groups based on a defined algorithm. Inclusion in the <100% adherence group resulted when one of the following criteria were met: 1) the participant reported taking his medication less times than prescribed in the last 4 days; 2) the participant always took his medication at the times prescribed in the last 4 days but this was not a typical pattern; or 3) the participant took fewer pills per dose than prescribed. Any response indicating less than perfect adherence by this algorithm would lead to inclusion in the less than 100% adherence group. This algorithm was applied to each specific drug. Overall, 100% adherence was defined as taking all doses and numbers of pills as prescribed for current medications. If a participant was less than 100% adherent for at least one of the medications taken within 4 days of the study visit, they were included in the lower adherence group. This strict adherence cut-off was based on U.S.A. panel guidelines stating that anything < excellent adherence may result in a virus breakthrough or the emergence of drug-resistant strains (5).

All participants with less than 100% adherence were asked to respond to a detailed list of reasons for missing their medications. Possible responses to each reason were never, rarely, sometimes and often. Responses were compiled and scored: never = 0, rarely = 1, sometimes = 2, and often = 3. Each of the 15 possible reasons received an overall score that was then computed into a mean score after taking the sample size into account.

Potential Determinants

Multiple factors and behaviors were examined for their association with < 100% adherence, both as predictors and as correlates of adherence. Self-reported race and level of education completed were obtained at study entry. Other characteristics examined as potential determinants or predictors of lower adherence were from the study visit 6 months prior to when the adherence data were captured (MACS visit 29, April 1998–October 1998). These variables included sociodemographics (age, employment, income), behavioral characteristics (alcohol use, recreational drug use, smoking), health care use (medical insurance coverage, outpatient medical care), and psychological covariates (depression, cognitive decline, QOL).

Depression was assessed with the Center for Epidemiologic Studies Depression Scale (CES-D Scale) shown to have high test-retest reliability and good predictive value for clinical depression (20,21). A conventional definition of depression (total CES-D Scale score of > 16) was used to indicate that the participant was depressed (22). Cognitive decline was assessed using the neuropsychological evaluations from the Symbol Digit Modalities test (SDMT) (23) and the Trailmaking test Parts A and B (24). For this analysis, raw test scores were transformed using published normative data stratified for age and education (25). Cognitive impairment was defined as at least 1.5 standard deviations (SDs) below the mean on any one of three test scores. The SF-36 Item Health Survey (26) was a self-administered instrument used to measure QOL on eight domains: physical functioning, bodily pain, physical role limitations, emotional role limitations, mental health, social functioning, energy/fatigue, and health perceptions. Scores from each domain were calculated according to the manual and interpretation guide (27). HIV disease stage defined by clinical symptoms, HIV-1 plasma RNA level and number of $CD4^+$ cells/mm^3 also was examined.

Potential correlates of adherence were collected at the same visit that adherence data were collected. All characteristics previously identified were examined for possible correlation with the medication adherence level. In addition, the total number of ART medications taken concurrently were examined to assess their influence on adherence as well as the length of time each individual reported receiving each antiretroviral medication.

The HIV RNA was quantified using either the Roche Amplicor RNA kit (Hoffman-LaRoche, Nutley, NJ, U.S.A.) with a detection limit of 400 copies/ml or the Roche Ultrasensitive RNA PCR assay (Hoffman-LaRoche, Nutley, NJ, U.S.A.), which has a detection limit of 50 copies/ml. All laboratories were certified by Roche for polymerase chain reaction (PCR). The HIV RNA measured at Visit 30 was used for the validation analyses. Enumeration of $CD4^+$ T-cell numbers were conducted on whole blood collected in EDTA using a Becton Dickinson Immunocytometry Systems, Inc. (BD, Franklin Lakes, NJ, U.S.A.) flow cytometer and BD monoclonal antibodies (28,29).

HIV Medications

Anti-HIV medications contained in this analysis included: 1) nucleoside reverse transcriptase inhibitors (zidovudine [ZDV], didanosine [ddI], zalcitabine [ddC], stavudine [d4T], lamivudine [3TC], abacavir [ABC], vistide [VIS], PMPA and adefovir [ADE]); 2) nonnucleoside reverse transcriptase inhibitors (nevirapine [NVP], delaviridine [DLV] and efavirenz [EFV]); and 3) protease inhibitors (saquinavir [SQV], indinavir [IDV], ritonavir [RTV], nelfinavir [NFV], and amprenavir [AMP]). Several of these medications (i.e., vistide, PMPA, lopinavir and adefovir) have not yet been approved by the U.S. federal Food and Drug Administration (FDA) but were included in this analysis. Medications that were taken as part of a clinical trial were included in the overall analysis and also evaluated separately. In addition to examining the ART medications independently, the medications were assessed by prescribed combinations to describe adherence by therapeutic regimen. Highly active antiretroviral therapy (HAART) was defined according to the 1997 U.S. National Institute of Heath Guidelines (30) as two or more NRTIs with either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor. Other drug use parameters that were assessed included conflicting instructions and use of a drug holiday defined as missing at least 2 consecutive days of all ARTs. There was no distinction made between a strategic treatment interruption (STI) and a self-prescribed lapse in therapy.

Statistical Analyses

The HIV RNA was compared with the self-reported adherence as a means of supporting the validity of the self-report. The proportions in each of the two adherence groups with undetectable plasma HIV RNA (< 50 copies/ml) were compared. Statistical significance of the difference was determined using a X^2 test. The magnitude of the univariate association between medication adherence and selected factors and behaviors was measured by ORs obtained with separate logistic regression models. Stratified analyses were used to examine the complex relationships between variables and appropriate multivariate logistic regression models were used to control for simultaneous confounding. Variables were selected for inclusion in the multivariate model based on their significance (e.g., $p < .05$) in univariate analysis.

RESULTS

Use of Antiretroviral Therapies

At Visit 30 (October 1998–March 1999), 539 HIV-1–seropositive MACS participants reported using ART and were interviewed about their adherence to their medications. The population consisting of 360 men who were seropositive at study entry and 179 seroconverters was 83.5% white non-Hispanic, 49.7% were >45 years old, 69.1% had a CD4 count > 350 cells/mm^3 and 52.2% had an undetectable HIV RNA (i.e., < 50 copies/ml). At study entry, these men had a median age of 31.3 years compared with the entire MACS cohort with a median age of 32.6 years and 83.3% white non-Hispanic. Of these men, 130 (24.1%) had been previously diagnosed with an opportunistic illness or malignancy definitive of AIDS (31). The total number of antiretroviral medications reported by these men at the time of their visit 30 clinic visit was 1586; 45.6% of the men were taking three medications simultaneously, 22.5% were taking four, 18.7% were taking two, 8.6% were taking five or more, and only 4.6% reported monotherapy. Overall, 466 (86.5%) of the participants were using a HAART regimen whereas only 8.6% were on a combination of therapies other than HAART. Of the 1586 reported medications, 99 (6.2%) were being taken as part of a clinical trial by 31 people. Adherence was slightly improved for drugs monitored in a research trial setting versus a nonresearch setting; 89.9% of those drugs used in a clinical setting had 100% adherence compared with 84.7% adherence for the other medications prescribed ($p = .16$). An examination by individual revealed similar results; 83.9% of those in a clinical trial versus 77.1% of those not in a clinical trial ($p = .40$) had 100% adherence. The analysis was done by specific medication, in addition to individual, because in many cases lower adherence to

one drug in a multidrug regimen did not mean lower adherence across all drugs. Because there was no significant difference, all individuals and medications were included in this analysis.

The frequency of the self-report ART medications is shown in Figure 1. The most commonly used medications were 3TC, d4T, IDV, and ZDV. Twenty-eight percent of the total 3TC use and 60% of the total ZDV use were taken as the combination tablet Combivir.

The 539 men reported 160 unique antiretroviral regimens. The most common combination therapy (ZDV, 3TC, and IDV) was used by 69 men, followed in frequency by the combination d4T, 3TC, and IDV (Fig. 2). Because of the large number of combinations reported in this cohort, only combinations taken by at least 10 men were included in the analysis by regimen.

Overall Adherence

Using the definition of adherence described above, 419 (77.7%) of the participants reported 100% adherence and 120 (22.3%) reported less than 100% adherence. Most of the men with lower adherence had missed a prescribed dosage during the last 4 days (19.7%; n = 106). Typically, this did not mean that medications were missed across all 4 days. Only 31 of the 106 men missed doses on all 4 days. Although 64 men reported taking fewer pills per dose than prescribed, most of these participants (n = 50) were already categorized in the lower adherent group based on missing an entire dose.

Reasons for missing medications were numerous but could easily be grouped into three main categories. The most commonly cited reasons related to an alteration in schedule such as a change in daily routine, busy with other things, or being away from home. The next grouping of reasons were associated with side effects, toxicity, illness and depression and the final group was related to difficulties taking the pills due to either the large numbers of pills to take and/or conflicting instructions. Detailed reasons for missing medications in order of frequency and mean score can be found in Table 1.

Many antiretroviral medications have specific instructions such as "take with food," "take on an empty stomach," or "take with plenty of fluids" to be strictly followed to ensure the effectiveness of the drug. In this cohort, 397 (74.1%) reported that they were required to follow these necessary instructions. Of these men, 71% reported always following the instructions. Only 24 men reported that they followed the instructions half the time or less. However, 92 men (23%) noted that their instructions conflicted among the drugs within their regimen.

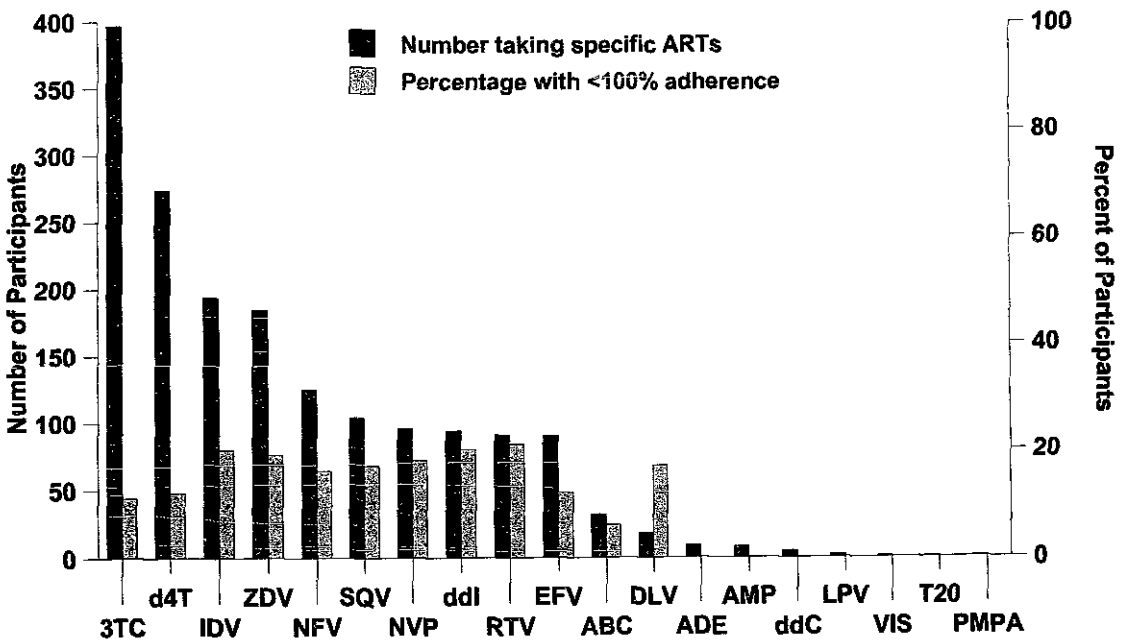

FIG. 1. Frequency of medication usage and proportion with <100% adherence by individual antiretroviral therapy (ART). Number of participants who took each ART is represented by *black bars* and interpreted on the left vertical axis. Percentage of those participants who were defined as <100% adherent is represented by *gray bars* and interpreted on the right vertical axis.

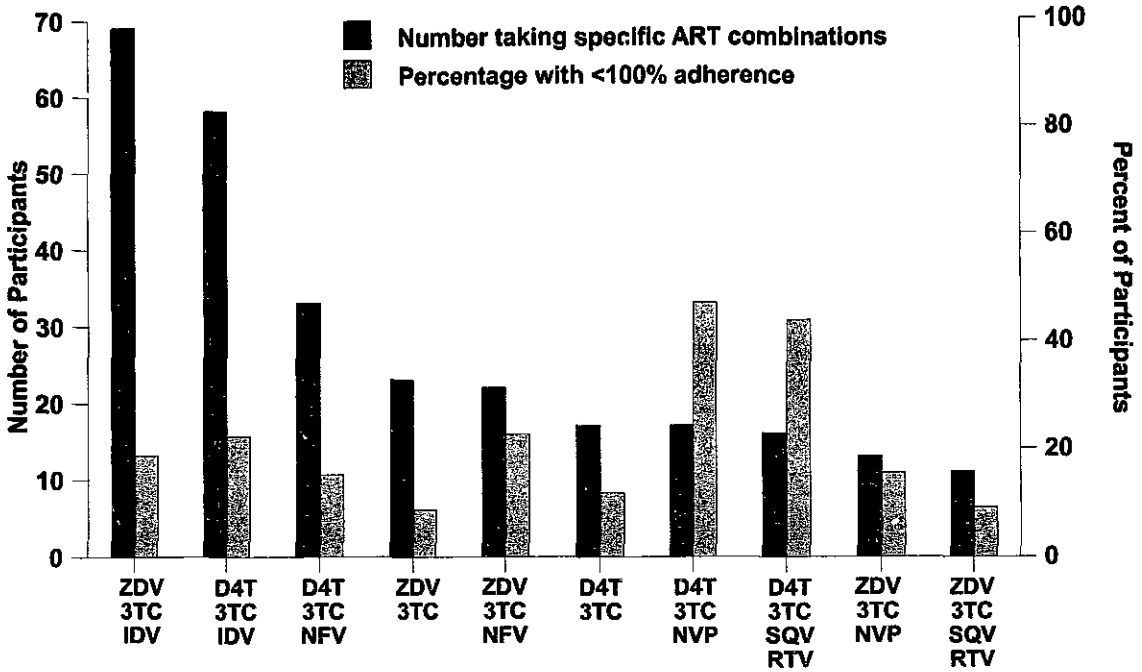

FIG. 2. Type and frequency of antiretroviral therapy combinations and proportion with <100% adherence by specific combination. Number of participants using each combination is represented by the *black bars* and interpreted on the left vertical axis. Percentage of those participants who were defined as <100% adherent is represented by *gray bars* and interpreted on the right vertical axis.

Validity of Self-Reported Adherence

HIV RNA measurements were performed on blood collected at the same time the adherence data were captured and therefore could help serve as validation of the self-reported data. A proportion of the cohort had not been tested using the ultrasensitive assay and therefore could not be evaluated at the cutoff of 50 copies/ml (n = 147). Among the remaining 393 men, 48.2% of the 100% adherent group had undetectable virus in their plasma versus 33.7% of the lower adherent group (p = .015). Among HAART users, the proportion with undetectable HIV RNA was greater in both groups (53.3% in the adherent group versus 37.4% in the lower adherent group) but remained significantly different (p = .013). Overall, when the HIV RNA level was evaluated using a higher detection threshold of 400 copies/ml, there were 64.4% with undetectable virus in the 100% adherent group versus 58.3% in the lower adherent group (p = .26).

TABLE 1. *Reasons for missing medications*

Reason	Mean score
Simply forgot	0.75
Had a change in daily routine	0.75
Was busy with other things	0.70
Was away from home	0.60
Don't want to take pills	0.53
Wanted to avoid side effects	0.48
Slept through dosing time	0.48
Felt like the drug was toxic or harmful	0.34
Ran out of pills	0.30
Felt depressed or overwhelmed	0.29
Felt sick or ill	0.28
Had too many pills to take	0.26
Have special instructions that conflict	0.22
Did not want others to notice	0.20
Had problems taking the pills	0.17

To observe whether there was a dose response, the group with the poorest adherence (defined as missing at least one dose across all 4 days) was compared with other men with less than perfect adherence. The poorest adherence group had 37.0% with undetectable levels of HIV RNA compared to 32.3% in the other <100% adherent group (p = .66). Therefore, no further gradations of the <100% adherent group were explored in this analysis.

A drug holiday was reported by 59 (10.9%) participants; of these men, 35 (59.3%) were in the lower ad-

herence group, whereas 24 (40.7%) were defined as 100% adherent. For men with lower adherence, a drug holiday was associated with higher levels of HIV RNA; 28.6% of those taking a drug holiday had HIV RNA levels < 50 copies/ml versus 36.0% for men not taking a drug holiday ($p = .49$). These proportions increased to 39.3% and 56.3% for HIV RNA levels < 400 copies/ml ($p = .13$). In contrast, there was no change in the level of HIV RNA for men who reported a drug holiday in the 100% adherent group (47.1% versus 48.2% with less than 50 copies/ml for drug holiday takers and nontakers, respectively, $p > .05$). Using a 400 copies/ml detection limit, these proportions increased to 70.6% and 56.7%, respectively ($p = .26$), indicating a possible benefit of drug holidays for men who were otherwise adherent.

Covariates Predicting Adherence

In the assessment of adherence by individual medication (Fig. 1), RTV, IDV, and ddI were associated with lower adherence but these differences were not statistically significant. A more meaningful assessment of adherence was by type of combination therapeutic regimen. The proportion of men with less than 100% adherence by treatment regimen is shown in Figure 2. There was a significant relationship between therapy combination and adherence. Of the 17 men reporting d4T, 3TC, and NVP and the 16 reporting d4T, 3TC, SQV, RTV, 47.1% and 43.8% were less adherent, respectively ($p < .05$) compared with the remaining frequency distribution. Combinations with the best adherence were ZDV and 3TC among whom only 8.7% men were lower adherers and RTV, SQV, 3TC, and ZDV of whom only 9.1% were less adherent.

The length of time that the patient had been taking the specific therapy also was examined as a determinant of adherence. Overall, 69.5% of the medications had been taken for > 6 months, 20.6% for 5 to 6 months, 3.4% for 3 to 4 months, 3.8% for 1 to 2 months, and 2.6% for < 1 month. Adherence did not significantly differ by categorizations of time on drug.

There was a direct relationship between the number of antiretroviral medications used concurrently and lower adherence (Table 2). For example, 37% of those who reported taking more than four antiretroviral medications reported lower adherence compared with 14.3% with low adherence among those taking one or two medications (OR, 3.40; $p = .002$). Of the men reporting three concurrent medications, 22.6% were in the lower adherent group (OR, 1.73; $p = .06$). Among men reporting the use of four medications, 24.8% had lower adherence (OR, 1.98; $p = .04$).

TABLE 2. *HIV-1 associated markers, symptoms, and therapy use*

	Total *N*	<100% *Adherence (%)*	Odds *ratio*	*p-value*
AIDS				
No	409	23.5	1.00	
Yes	130	18.5	0.74	.23
HIV-related symptoms				
No	214	23.4	1.00	
Yes	287	20.6	0.85	.45
Depression				
No	339	21.8	1.00	
Yes	104	25.0	1.19	.50
Cognitive decline				
No	306	23.2	1.00	
Yes	30	26.7	1.20	.67
CD4 number				
>350/mm^3	315	19.4	1.00	
≤350/mm^3	141	28.4	1.65	.03
HIV-1 RNA				
≥50 copies/ml	209	23.9	1.00	
<50 copies/ml	228	21.1	0.85	.47
Number of antiretroviral therapies:				
1–2	126	14.3	1.00	
3	246	22.6	1.73	.06
4	121	24.8	1.98	.04
>4	46	37.0	3.40	.002

An examination of the history of different HAART regimens from initiation of HAART to Visit 30 and the association with adherence was done. Of the 466 men on HAART, 31.6% were on their initial HAART regimen, 27.3% were on their second regimen, 19.5% on their third, 12.9% on their fourth, and 8.8% had at least five prior HAART regimens. Proportions with less than 100% adherence were 22.5%, 24.4%, 26.4%, 21.7%, and 19.5%, respectively. There was no significant association between the prior number of different HAART regimens and current medication adherence comparing men with a history of multiple regimens versus men on their initial regimen (OR, 1.08, $p = .74$).

As shown in Tables 2 and 3, significant univariate predictors of lower adherence were African-American race (OR, 2.3; $p = .005$), having an annual income <U.S.$50,000 (OR, 1.9; $p = .01$), a CD4 cell count less than 350 cells/mm^3 (OR, 1.65; $p = .03$), and no outpatient visit within the period 6 to 12 months prior to the visit (OR, 2.63; $p = .02$).

All covariates noted as significant in the univariate results, with the exception of CD4 cell count, remained significant ($p < .05$) determinants of lower adherence after simultaneously controlling for confounding in the multivariate logistic regression model. The ORs and 95% CIs from the final multivariate model are presented in Figure 3. There was a significant negative correlation between the CD4 cell count and increasing numbers of ART medications ($p = .01$). After stratifying for the number of ART medications, CD4 cell count was no longer a significant predictor of medication adherence.

TABLE 3. *Demographics and behavioral characteristics*

	Total *N*	<100% Adherence (%)	Odds ratio	*p*-value
Age (y)				
>45	268	21.6	1.00	
≤45 or younger	271	22.9	1.07	.73
Race				
Not African American	486	20.6	1.00	
African American	53	37.7	2.34	.005
Education				
College or more	300	20.7	1.00	
Less than college	233	24.9	1.27	.25
Employment				
Not full-time	178	22.5	1.00	
Full-time	274	22.3	0.99	.96
Income				
≥$50,000	165	15.2	1.00	
<$50,000	335	25.1	1.87	.01
Medical insurance				
Yes	474	21.9	1.00	
No	26	19.2	0.85	.74
Outpatient visit				
Yes	473	20.7	1.00	
No	27	40.7	2.63	.02
Smoking				
No	384	20.6	1.00	
Yes	117	25.6	1.33	.25
Alcohol (drinks/week)				
≤14	472	21.2	1.00	
>14	27	29.6	1.57	.30
Recreational drugs				
No	224	21.0	1.00	
Yes	277	22.4	1.09	.71

Covariates Correlating With Adherence

After controlling for simultaneous confounding in the multivariate logistic regression model, significant correlates of lower adherence included African-American race (OR, 2.2; $p = .005$), an annual income <U.S.$50,000 (OR, 2.6; $p = .001$), CES-D score >16 (OR, 1.8; $p = .03$), increasing numbers of ART medications taken concurrently (OR, 2.1; $p = .06$ for three medications; OR, 2.5; $p = .04$ for four medications and OR, 4.5; $p = .002$ for more than four medications). Correlates were measured at the same visit (Visit 30) as the adherence ascertainment, whereas factors assessed as predictors were measured at the prior visit (Visit 29).

DISCUSSION

Among the MACS participants, more than three quarters reported perfect adherence to their ART regimen as prescribed by their physicians. These self-reported adherence data tended to correlate with concomitant levels of HIV RNA. Medication adherence in this population is superior to what has been reported in other studies (32,33). However, it is important to keep in mind that this cohort has been observed during a 15-year follow-up, and that the 539 men in this analysis have persevered in the study through to its 30th semiannual visit. For example, 66% of the men in this analysis have attended at least 90% of their study visits. It would be expected that such extraordinary adherence to study protocol would also be reflected in terms of adherence to their medications. In addition, these men are highly educated, with 56% of the 539 men having completed at least a college degree at study entry. When medication doses were missed, the main reasons related primarily to a change in schedule such as a holiday or other deviations from the daily routine. Overall, few men reported frequent problems with taking their pills due to the large quantities or conflicting instructions, although adherence diminished with increasing numbers of ART medications.

There are several unique aspects of this study. First, the size of the cohort is large and well characterized for history of disease progression. Second, the adherence data in the MACS are not collected by the primary physician or in a monitored clinical trial setting so there is less reason to overreport adherence. Third, results are more likely to reflect homosexual men of similar demographics in the population.

Because there is no standard definition of medication adherence, it is difficult to compare rates of adherence across studies. Most studies use a ratio of doses taken to doses prescribed to define adherence but many have used a cutoff point of 80% to categorize patients as adherent and nonadherent (34). The 80% value is a threshold based on data from other chronic illnesses such as hypertension and diabetes (35). With the new potent regimens, this cutoff may be inappropriate. As indicated in the International AIDS Society—USA panel guidelines, anything less than excellent adherence may result in a virus breakthrough or the emergence of drug-resistant strains (5). Unfortunately, the degree of adherence to HAART that is necessary to prevent resistance is unknown and further research is urgently needed (13). Complete suppression of viral replication is not ensured with 80% adherence and special instructions for the medication usage need to be taken into account (i.e., absorption of ddI, SQV, RTV, IDV, and NFV are affected by adherence to special instructions). Although ART adherence rates vary considerably from study to study, many report levels closer to 60% in their populations when using thresholds of 80% to 90% to define acceptable levels of adherence (12,36,37). Given that our study defined adherence as total adherence (100%), the observation of 77% meeting this level is within the realm

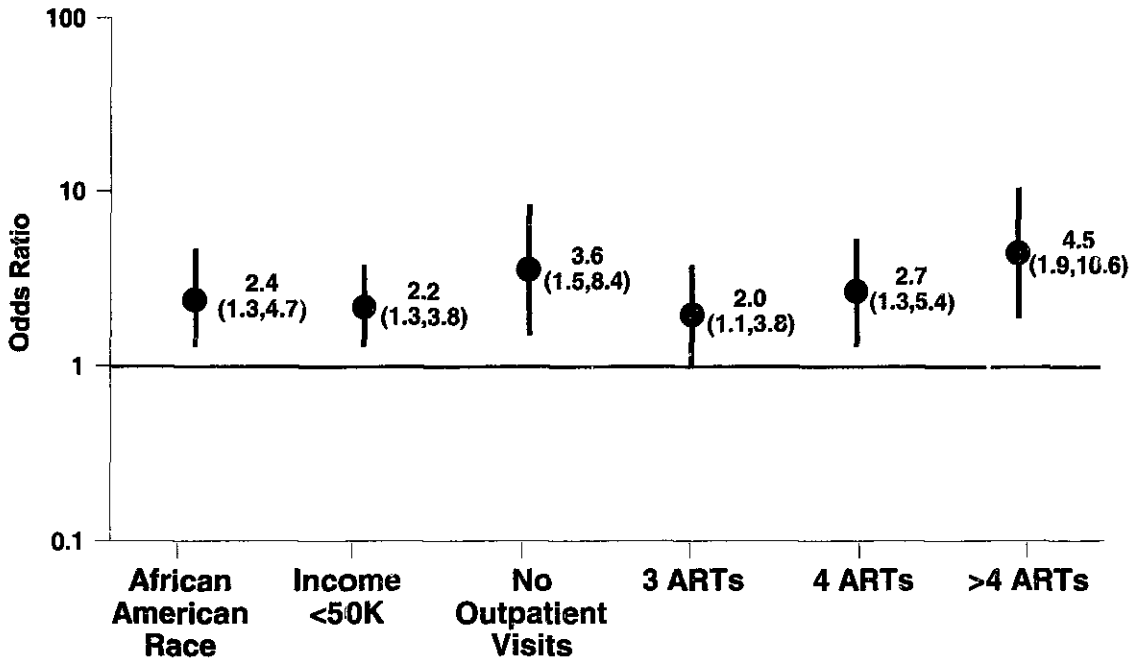

FIG. 3. Odds ratios (OR) and 95% confidence intervals for characteristics independently predictive of less than 100% adherence. The horizontal line (OR = 1) is provided as a reference indicating level of no association. ORs (large dots) are presented for African-American race compared with other races, incomes less than U.S.$50,000 compared with higher incomes, lack of outpatient visit compared with having had an outpatient visit, and use of increasing numbers of antiretroviral medications (i.e., 3, 4, and >4 compared with 1 or 2 medications). Results were obtained from a multivariate logistic regression model.

of findings from these other studies in which a lower threshold was used.

Despite the high levels of adherence in this cohort, we identified determinants of adherence heterogeneity, which included behavioral, sociodemographic, economic, and immunologic factors. In this cohort, African-American race, an annual income <U.S.$50,000, no recent outpatient visit, increasing numbers of ARTs taken concurrently and the specific combination of therapies were all independent determinants of lower adherence. In addition, those in the lower adherent category were more likely to be depressed, defined by a higher CES-D scale. However, given that this latter variable was determined concurrently, temporality cannot be discerned. Depression may have been a consequence of circumstances that also led to poorer adherence. However, other studies found an association between symptoms of depression and lower adherence to ART (12,37). Depressive behavior has historically been associated with self-neglect and forgetfulness, which would likely impact on adherence. In this study, we found no significant associations between any of the eight QOL domains examined and adherence. This is consistent with the results of at least one other study that measured patients' perceived quality of life (37).

The consistency of these findings with results from other studies gives credence to the validity of the relationships. The lower adherence by African Americans has been observed in several studies (32,35,37,38). Given that we observed an association with race in a cohort with a small proportion of nonwhites, this further strengthens the relationship of race and adherence. Lower medication adherence levels by race may be due to differences in health beliefs, social support structures, or mistrust of the health care system (39,40).

Although this study controlled for having an ambulatory visit, the lower adherence may further relate to the frequency of visitation. Fewer visits to their physicians means less clinical monitoring and less frequent refills of prescriptions. Given this situation, participants may extend their medications between visits by taking fewer pills than prescribed. This latter situation is also consistent with the association of lower adherence with lower incomes. However, rather than very low incomes defining this relationship, the lower incomes in our study refer mostly to those constituting middle incomes in the gen-

eral population. Therefore, lower adherence may either still relate to underlying host characteristics of people with these incomes or reflects a prioritization in the decision-making process. Again, a lower adherence may be a problem of lack of knowledge regarding health consequences in subgroups forced to make certain choices. The contribution of lower levels of socioeconomic status (SES) as measured by income to lower adherence could not be assessed comprehensively since men with very low SES are underrepresented in this cohort. Alternatively, there may be less understanding about implications of nonadherence in certain settings. However, these latter explanations are most unlikely in this cohort given the amount of scientific information provided to the participants from the study (41) and their high level of educational attainment.

Other studies have shown a significant relationship between illicit injecting drug use and lower adherence (12,37). Because only 10% of the entire MACS cohort reported ever injecting drugs and only 4 of the 539 men in this study currently inject drugs, this was not an attributable factor in this cohort.

In this study, we found specific drug combinations that were associated with lower adherence. Individuals prescribed the combination 3TC, SQV, RTV, and d4T had lower adherence. There are several possible explanations. It has been found clinically that RTV has more severe side effects than the other protease inhibitors and has multiple drug interactions, many of which are drugs that HIV patients commonly take (42). RTV has had several formulations. The capsules used during this study period required continual refrigeration, thus making it more difficult to take them while away from home. Although this formulation was changed during the summer of 1999, refrigeration is still recommended for temperatures exceeding 80°F. A liquid formulation that is known to have an offensive taste was also used during this data collection period. Additionally, this regimen contains four ART medications and we found that a therapeutic regimen containing more than three ART medications was associated with lower adherence. The other combination found to have a high proportion of lower adherers was d4T, 3TC, and NVP. This is difficult to explain since this combination requires taking only three capsules, twice a day. It may be likely that physicians would prescribe these medications for their patients known or suspected to have problems with adherence simply because this combination is known to have fewer obstacles that may affect adherence. Thus, this association may be an artifact due to selection bias. Decisions regarding which medications to prescribe are partially dependent on the physician's opinion of the patient's ability to adhere. In other words, physicians may "select" simpler regimens for patients who are deemed more likely to experience adherence problems, thereby artificially inflating the proportion with poorer adherence. In this study, the drug-specific rate of lower adherence for NVP was 18%, which is similar to the 15% rate reported in the INCAS trial (6). Despite the types of medications prescribed, it is expected that as the complexity of these regimens increases, so do the rates of nonadherence (36,43).

The lower adherence associated with the use of multiple medications speaks to a need for further development and use of pills in which multiple medications are formulated in one capsule or pill. Besides limiting the numbers of concurrent pills, there is less chance of conflicting instructions. Although some of these formulations are now on the market, continuing development is needed to facilitate adherence to dosage and other special instructions.

An intriguing finding was that a drug holiday was not virologically detrimental if the participant was otherwise perfectly adherent to his prescribed medications. However, the combination of lower adherence and a drug holiday was associated with increased plasma HIV RNA levels. It was not possible to determine whether the drug holiday was prescribed by the physician or selected by the participant. Given the difference in viral load by adherence levels, it is likely that the characterization of the drug holiday by prescription or duration may differ between the groups. It has been reported that it may be better to stop all drugs rather than reduce the dose or discontinue only one medication in the regimen. Reductions versus halting drugs may result in a higher rate of resistance mutations (44). Partial suppression is dangerous, allowing the development of mutations in a replicating population of the virus and has the highest probability of resistant strains. This situation occurs when a patient takes some of his drugs, some of the time. A patient who is either 0% compliant or 100% compliant is less likely to contribute to the pool of resistant virus (11). It will be important to examine the virologic and clinical impact of the duration of drug holidays.

In summary, the medication adherence questionnaire discriminated adherence to ART ascertained by self-reported data. Perfect adherence was supported by a higher proportion of individuals with undetectable plasma HIV RNA. Linking self-reported adherence data to HIV viremia suggests that these self-reported data are a valid indicator of adherence and supports the validity of a questionnaire as a useful tool in large observational studies. However, several studies have shown that self-reports of adherence tend to overestimate true adherence levels (45). An intriguing finding was that a drug holiday

was not virologically detrimental if the participant was otherwise perfectly adherent to his prescribed medications. Despite the high level of adherence, socioeconomic factors significantly discriminated lower adherence in this cohort. Considering the role that adherence plays for clinical effectiveness of ART, identification of individuals with characteristics associated with lower adherence provides the basis for interventions to enhance adherence and thereby optimize the benefit of effective therapies. Patients with these characteristics (i.e., African-American race, no recent outpatient visit, concurrent use of more than three ART medications, lower incomes, and depression) should be targeted with special efforts to increase adherence.

APPENDIX

The Multicenter AIDS Cohort Study (MACS) members include:

Baltimore: The Johns Hopkins University School of Hygiene and Public Health: Joseph B. Margolick, principal investigator; Haroutune Armenian; Homayoon Farzadegan; Nancy Kass; Justin McArthur; Steffanie Strathdee; Ellen Taylor.

Chicago: Howard Brown Health Center and Northwestern University Medical School: John P. Phair, principal investigator; Joan S. Chmiel: Bruce Cohen; Maurice O'Gorman; Daina Variakojis; Steven M. Wolinsky.

Los Angeles: University of California Los Angeles Schools of Public Health and Medicine: Roger Detels, principal investigator; Janis V. Giorgi, principal investigator; Beth Jamieson, principal investigator; Barbara R. Visscher, coprincipal investigator; Eric G. Bing; John Fahey; John Ferbas; Otoniel Martínez-Maza; Eric N. Miller; Hal Morgenstern; Pari Nishanian; John Oishi; Paul Satz; Elyse Singer; Jeremy Taylor; Harry Vinters; Dorothy Wilcy; Stephen Young.

Pittsburgh: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo, principal investigator; Lawrence Kingsley, coprincipal investigator; James T. Becker; Phalguni Gupta; John Mellors; Sharon Riddler; Anthony Silvestre.

Data Coordinating Center: The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland: Alvaro Muñoz, principal investigator; Lisa P. Jacobson, coprincipal investigator: Linda Ahdieh; Stephen Gange; Cynthia Kleeberger; Steven Piantadosi; Ellen Smit; Sol Su; Patrick Tarwater.

U.S. National Institutes of Health: National Institute of Allergy and Infectious Diseases: Carolyn Williams, project officer; Paolo Miotti. National Cancer Institute: Sandra Melnick.

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